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# *Guest Editorial*

## AQUAPORINS ACQUIRE NOBEL

The most recent Nobel Prize in Chemistry (2003) honours two American physicians-turned-bench-scientists for their work illuminating how ions and water molecules move in and out of cells. *Dr. Roderick MacKinnon* has been recognized for working out the atomic structure of an ion channel and *Dr. Peter Agre* for discovering that a major protein found in red blood cells functions primarily as a water channel.

That the body's cells must contain specific channels for transporting water was suspected as early as the middle of the nineteenth century. The literature constantly referred to "Water channel" based on functional, biophysical and morphologic data. However, it was not until 1988 that Peter Agre succeeded in isolating a membrane protein that, a year or so later, he realized must be the long-sought-after water channel. Agre went on to establish the family of related channels, which he named "aquaporins."

Aquaporins form a large, diverse family of proteins and have been found in bacteria, plants, and animals. Less than a decade ago, scientists discovered the aquaporin Z gene (AqpZ) in *E. coli,* pointing to the protein's role in regulating water transport in this prokaryote. The aquaporin Z channel protein in *E. coli* can accommodate a flow of water at very high rates. After producing a recombinant form of AqpZ in *E. coli,* the proteins were first crystallized (capturing five water molecules inside) and then analyzed by state-of-the-art high-resolution X-ray diffraction techniques. The architecture of aquaporin Z is typical of aquaporins, with a spiral of eight oxygens providing water-binding sites inside the channel. The outer membrane and cytoplasmic ends of the channel are wider than the interior, which is long and narrow. This structure demonstrates that aquaporin selectivity arises in part from erecting a physical barrier: small molecules, like water, can easily pass, but larger ones simply cannot fit. The strategic positioning of amino acid residues with hydrophilic or hydrophobic properties along the channel helps police the influx of molecules based on their affinity for water. While it seems two amino acid chains located in the middle of the channel also provide a water-friendly surface, scientists believe that they play a more intriguing role. Noting that the water molecules occupy the channel in single file, the scientists explain that such an orientation would normally facilitate the random flow of protons (or hydrogen ions), which would be lethal to the cell. This central amino acid pair, they say, restricts the behavior of water molecules in the center of the channel in such a way that prevents "proton jumping", yet keeps the water flowing. With the structural models of aquaporins down to the atomic level being available, scientists can now begin to investigate the molecular mechanisms that facilitate their selectivity.

In mammals ten isomers of Aquaporins (AQPO-AQP9) have been isolated till date. Residue Cystine 189 in AQP-1 is the site of action of mercurial water transport inhibitor used in all the physiological studies. Even though largely aquaporins are water selective, recently AQP-1 has been shown to be permeable to carbon dioxide and AQP-3 and AQP-9 to small solutes like urea and glycerol. Based on these properties and phylogenetic consideration, Peter Agre and his colleagues recently have allocated some of the channels into one of the two groups: *Orthodox set* (aquaporins) and *Cocktail set* (aquaglyceroporins). The studies like antibody localization of proteins, Northern blot analysis and *in-situ* hybridization based localization of transcripts have demonstrated that these channels are present in wide variety of cell types.

The discovery of aquaporin is an example of luck favoring the well-prepared mind. Beginning in the mid-1980s, Peter Agre and his colleagues, including technician Barbara Smith and then post-doc Gregory Preston were searching for proteins that are part of the Rh-factor when they came across an abundant and much smaller protein. The researchers pursued the unexpected protein visitor; they isolated it and discovered that it was widely expressed, and within a year had cloned its complementary DNA. In dramatic experiments with frog's eggs, the scientists next proved that the unknown protein was in fact biology's elusive cellular regulator of water transport.

This decisive discovery has ushered in a golden age of biochemical, physiological and genetic studies of these proteins in bacteria, plants and mammals. These studies have helped in the understanding - at the molecular level - of malfunctioning of these channels associated with many diseases of the kidneys, skeletal muscle and other organs. There are few human diseases in which mutation of aquaporins have been described. The role of AQP-2 mutation in nephrogenic diabetes insipidus has been studied quite intensely. The aquaporin knockout mice experiments (developed by Verkman et al.) have produced a novel insight in understanding the role of aquaporins in the physiology of many organ systems. Working from this basic knowledge, scientists are searching for drugs that can specifically target water channel defects.

The importance of this discovery is very aptly stated by Peter Agre himself: "I am certain that in the future, we will be able to capitalize on our understanding of aquaporins to benefit medicine, biotechnology and even agriculture". He further adds, "We still have much to learn, and the possibilities of where aquaporins will take us are unlimited".

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